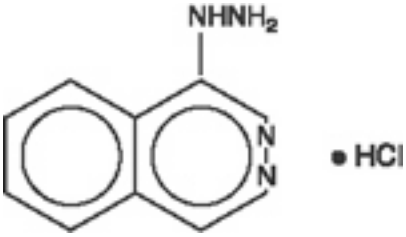
TRAMADOL HYDROCHLORIDE - tramadol hydrochloride tablet, extended release
Par Pharmaceutical Inc.

DESCRIPTION

Tramadol hydrochloride is a centrally acting synthetic analgesic in an extended-release formulation. The chemical name is (±) cis-2-[(dimethylamino)methyl]--1-(3-methoxyphenyl) cyclohexanol hydrochloride. Its structural formula is:



The molecular weight of tramadol hydrochloride is 299.8. It is a white, bitter, crystalline and odorless powder that is readily soluble in water and ethanol and has a pKa of 9.41. The n-octanol/water log partition coefficient (logP) is 1.35 at pH 7. Tramadol hydrochloride Extended-Release (ER) tablets contain 100 mg or 200 mg of tramadol hydrochloride in an extended-release formulation. The tablets are white to off-white in color and contain the inactive ingredients colloidal silicone dioxide, dibutyl sebacate, ethylcellulose, magnesium stearate, polyvinyl alcohol, povidone K-90, and an imprinting agent, Opacode S-1-17823 black, which contains the following ingredients: shellac, iron oxide black, isopropyl alcohol, n-butyl alcohol, propylene glycol, and ammonium hydroxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Tramadol hydrochloride is a centrally acting synthetic opioid analgesic. Although its mode of action is not completely understood, from animal tests, at least two complementary mechanisms appear applicable: binding of parent and M1 metabolite to μ-opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin.
Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to μ-opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ-opioid binding. Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone in several animal tests. The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound.
Tramadol has been shown to inhibit reuptake of norepinephrine and serotonin *in vitro*, as have some other opioid analgesics. These mechanisms may contribute independently to the overall analgesic profile of tramadol. The relationship between exposure of tramadol and M1 and efficacy has not been evaluated in the tramadol hydrochloride ER tablets clinical studies.
Apart from analgesia, tramadol administration may produce a constellation of symptoms (including dizziness, somnolence, nausea, constipation, sweating and pruritus) similar to that of other opioids. In contrast to morphine, tramadol has not been shown to cause histamine release. At therapeutic doses, tramadol has no effect on heart rate, left-ventricular function or cardiac index. Orthostatic hypotension has been observed.

Pharmacokinetics

The analgesic activity of tramadol is due to both parent drug and the M1 metabolite. Tramadol hydrochloride ER tablet is administered as a racemate and both the [-] and [+] forms of both tramadol and M1 are detected in the circulation.
The pharmacokinetics of tramadol hydrochloride ER tablets are approximately dose-proportional over a 100 to 400 mg dose range in healthy subjects. The observed tramadol AUC values for the 400 mg dose were 26% higher than predicted based on the AUC values for the 200 mg dose. The clinical significance of this finding has not been studied and is not known.

Absorption

In healthy subjects, the bioavailability of a tramadol hydrochloride ER 200 mg tablet relative to a 50 mg every six hours dosing regimen of the immediate-release dosage form (tramadol hydrochloride) was approximately 85 to 90%. Consistent with the extended-release nature of the formulation, there is a lag time in drug absorption following tramadol hydrochloride ER tablets administration. The mean peak plasma concentrations of tramadol and M1 after administration of tramadol hydrochloride ER tablets to healthy volunteers are attained at about 12 hours and 15 hours, respectively, after dosing (see Table 1 and Figure 2). Following administration of the tramadol hydrochloride ER tablet, steady-state plasma concentrations of both tramadol and M1 are achieved within four days with once daily dosing.

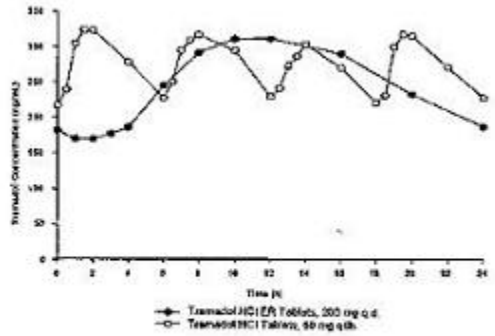
The mean (%CV) pharmacokinetic parameter values for tramadol hydrochloride ER tablet 200 mg administered once daily and tramadol hydrochloride immediate-release 50 mg administered every six hours are provided in **Table 1**.

Table 1. Mean (%CV) Steady-State Pharmacokinetic Parameter Values (n=32)

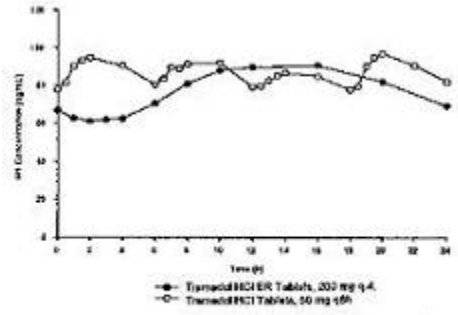
	Tramadol	M1 Metabolite

Pharmacokinetic Parameter	Tramadol HCl ER 200 mg Tablet OnceDaily	Tramadol HCl50 mg Tablet Every 6 Hours	Tramadol HCl ER 200 mgTablet OnceDaily	Tramadol HCl50 mgTablet Every 6Hours
AUC_{0-24} (ng.h/mL)	5975 (34)	6613 (27)	1890 (25)	2095 (26)
C_{max} (ng/mL)	335 (35)	383 (21)	95 (24)	104 (24)
C_{min} (ng/mL)	187 (37)	228 (32)	69 (30)	82 (27)
T_{max} (h)	12 (27)	1.5 (42)	15 (27)	1.9 (57)
% Fluctuation	61 (57)	59 (35)	34 (72)	26 (47)
AUC_{0-24}: Area Under the Curve in a 24 hour dosing interval; C_{max}: Peak Concentration in a 24 hour dosing interval; C_{min}: Trough Concentration in a 24 hour dosing interval; T_{max}: Time to Peak Concentration				

Figure 2: Mean Steady-State Tramadol (a) and M1 (b) Plasma Concentrations on Day 8 Post Dose after Administration of 200 mg Tramadol Hydrochloride ER Tablet Once Daily and 50 mg Tramadol Hydrochloride Tablets Every 6 Hours.



a. Tramadol



b. M1

Food Effects

After a single dose administration of 200 mg tramadol hydrochloride ER tablet with a high fat meal, the C_{max} and $AUC_{0-\infty}$ of tramadol decreased 28% and 16%, respectively, compared to fasting conditions. Mean T_{max} was increased by 3 hour (from 14 hour under fasting conditions to 17 hour under fed conditions). While tramadol hydrochloride ER tablet may be taken without regard to food, it is recommended that it be taken in a consistent manner.

Distribution

The volume of distribution of tramadol was 2.6 and 2.9 liters/kg in male and female subjects, respectively, following a 100 mg intravenous dose. The binding of tramadol to human plasma proteins is approximately 20% and binding also appears to be independent of concentration up to 10 mcg/mL. Saturation of plasma protein binding occurs only at concentrations outside the clinically relevant range.

Metabolism
Tramadol is extensively metabolized after oral administration. The major metabolic pathways appear to be N – (mediated by CYP3A4 and CYP2B6) and O – (mediated by CYP2D6) demethylation and glucuronidation or sulfation in the liver. One metabolite (O-desmethyl tramadol, denoted M1) is pharmacologically active in animal models. Formation of M1 is dependent on CYP2D6 and as such is subject to inhibition, which may affect the therapeutic response (see **PRECAUTIONS - Drug Interactions**).

Elimination
Tramadol is eliminated primarily through metabolism by the liver and the metabolites are eliminated primarily by the kidneys. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The remainder is excreted either as unidentified or as unextractable metabolites. The mean terminal plasma elimination half-lives of racemic tramadol and racemic M1 after administration of tramadol hydrochloride ER tablets are approximately 7.9 and 8.8 hours, respectively.

Special Populations

Renal
Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. The pharmacokinetics of tramadol were studied in patients with mild or moderate renal impairment after receiving multiple doses of tramadol hydrochloride ER tablets 100 mg. There is no consistent trend observed for tramadol exposure related to renal function in patients with mild (CLcr: 50 to 80 mL/min) or moderate (CLcr: 30 to 50 mL/min) renal impairment in comparison to patients with normal renal function. However, exposure of M1 increased 20 to 40% with increased severity of the renal impairment (from normal to mild and moderate). Tramadol hydrochloride ER tablets have not been studied in patients with severe renal impairment (CLcr < 30 mL/min). The limited availability of dose strengths of tramadol hydrochloride ER tablets does not permit the dosing flexibility required for safe use in patients with severe renal impairment. Therefore, tramadol hydrochloride ER tablets should not be used in patients with severe renal impairment (see **PRECAUTIONS - Use in Renal and Hepatic Disease** and **DOSAGE AND ADMINISTRATION**). The total amount of tramadol and M1 removed during a 4 hour dialysis period is less than 7% of the administered dose.

Hepatic
Pharmacokinetics of tramadol was studied in patients with mild or moderate hepatic impairment after receiving multiple doses of tramadol hydrochloride ER tablets 100 mg. The exposure of (+)- and (-)-tramadol was similar in mild and moderate hepatic impairment patients in comparison to patients with normal hepatic function. However, exposure of (+)- and (-)-M1 decreased ~50% with increased severity of the hepatic impairment (from normal to mild and moderate). The pharmacokinetics of tramadol after the administration of tramadol hydrochloride ER tablets has not been studied in patients with severe hepatic impairment. After the administration of tramadol immediate-release tablets to patients with advanced cirrhosis of the liver, tramadol area under the plasma concentration time curve was larger and the tramadol and M1 half-lives were longer than subjects with normal hepatic function. The limited availability of dose strengths of tramadol hydrochloride ER tablets does not permit the dosing flexibility required for safe use in patients with severe hepatic impairment. Therefore, tramadol hydrochloride ER tablets should not be used in patients with severe hepatic impairment (see **PRECAUTIONS - Use in Renal and Hepatic Disease** and **DOSAGE AND ADMINISTRATION**).

Geriatric
The effect of age on the absorption of tramadol from tramadol hydrochloride ER tablets in patients over the age of 65 years has not been studied and is unknown (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Gender
Based on pooled multiple-dose pharmacokinetics studies for tramadol hydrochloride ER tablets in 166 healthy subjects (111 males and 55 females), the dose-normalized AUC values for tramadol were somewhat higher in females than in males. There was a considerable degree of overlap in values between male and female groups. Dosage adjustment based on gender is not recommended.

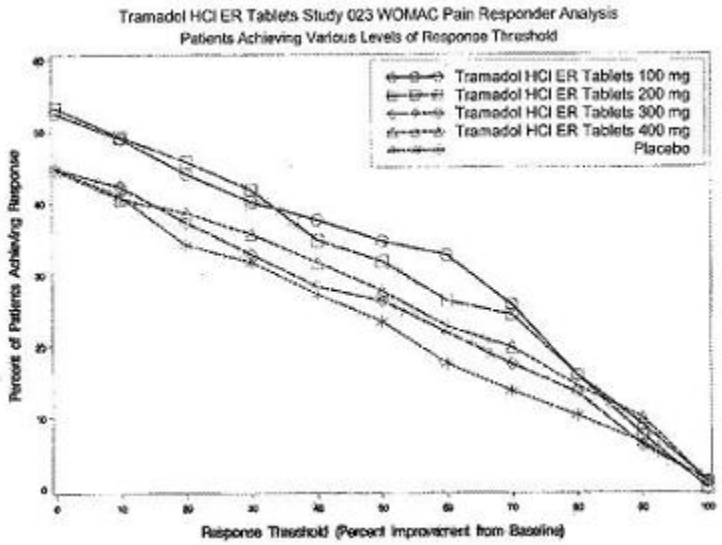
Drug Interactions
The formation of the active metabolite, M1, is mediated by CYP2D6. Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P-450. Based on a population PK analysis of Phase I studies with immediate-release tablets in healthy subjects, concentrations of tramadol were approximately 20% higher in "poor metabolizers" versus "extensive metabolizers," while M1 concentrations were 40% lower. *In vitro* drug interaction studies in human liver microsomes indicate that inhibitors of CYP2D6 (fluoxetine, norfluoxetine, amitriptyline, and quinidine) inhibit the metabolism of tramadol to various degrees, suggesting that concomitant administration of these compounds could result in increases in tramadol concentrations and decreased concentrations of M1. The full pharmacological impact of these alterations in terms of either efficacy or safety is unknown.
Tramadol is also metabolized by CYP3A4. Administration of CYP3A4 inhibitors, such as ketoconazole and erythromycin, or inducers, such as rifampin and St. John’s Wort, with tramadol hydrochloride ER tablets may affect the metabolism of tramadol leading to altered tramadol exposure (see **PRECAUTIONS - Drug Interactions**).

Quinidine
Tramadol is metabolized to M1 by CYP2D6. A study was conducted to examine the effect of quinidine, a selective inhibitor of CYP2D6, on the pharmacokinetics of tramadol by administering 200 mg quinidine two hours before the administration of tramadol hydrochloride ER tablets 100 mg. The results demonstrated that the exposure of tramadol increased 50 to 60% and the exposure of M1 decreased 50 to 60% (see PRECAUTIONS - Drug Interactions). In vitro drug interaction studies in human liver microsomes indicate that tramadol has no effect on quinidine metabolism.

Carbamazepine
Carbamazepine, a CYP3A4 inducer, increases tramadol metabolism. Patients taking carbamazepine may have a significantly reduced analgesic effect of tramadol. Because of the seizure risk associated with tramadol, concomitant administration of tramadol hydrochloride ER tablets and carbamazepine is not recommended (see **PRECAUTIONS** - **Drug Interactions**).

Cimetidine
Concomitant administration of tramadol immediate-release tablets with cimetidine does not result in clinically significant changes in tramadol pharmacokinetics. No alteration of the tramadol hydrochloride ER tablets dosage regimen with cimetidine is recommended.

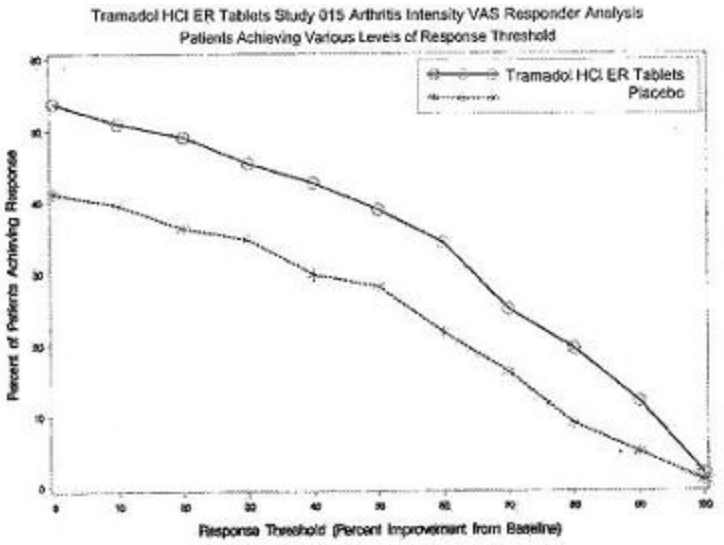
CLINICAL STUDIES
Tramadol hydrochloride ER tablets were studied in patients with chronic, moderate to moderately severe pain due to osteoarthritis and/or low back pain in four 12 week, randomized, double-blind, placebo-controlled trials. To qualify for inclusion into these studies, patients were required to have moderate to moderately severe pain as defined by a pain intensity score of ≥40 mm, off previous medications, on a 0 to 100 mm visual analog scale (VAS). Adequate evidence of efficacy was demonstrated in the following two studies:
In one 12 week randomized, double-blind, placebo-controlled study, patients with moderate to moderately severe pain due to osteoarthritis of the knee and/or hip were administered doses from 100 mg to 400 mg daily. Treatment was initiated at 100 mg QD for four days then increased by 100 mg per day increments every five days to the randomized fixed dose. Between 51% and 59% of patients in the tramadol hydrochloride ER tablets treatment groups completed the study and 56% of patients in the placebo group completed the study. Discontinuations due to adverse events were more common in tramadol hydrochloride ER tablets 200 mg, 300 mg and 400 mg treatment groups (20%, 27%, and 30% of discontinuations, respectively) compared to 14% of the patients treated with tramadol hydrochloride ER tablets 100 mg and 20% of patients treated with placebo.
Pain, as assessed by the WOMAC Pain subscale, was measured at 1, 2, 3, 6, 9, and 12 weeks and change from baseline assessed. A responder analysis based on the percent change in WOMAC Pain subscale demonstrated a statistically significant improvement in pain for the 100 mg and 200 mg treatment groups compared to placebo (see Figure 3).
Figure 3



In one 12 week randomized, double-blind, placebo-controlled flexible-dosing trial of tramadol hydrochloride ER tablets in patients with osteoarthritis of the knee, patients titrated to an average daily tramadol hydrochloride ER tablets dose of approximately 270 mg/day. Forty-nine percent of patients randomized to tramadol hydrochloride ER tablets completed the study, while 52% of patients randomized to placebo completed the study. Most of the early discontinuations in the tramadol hydrochloride ER tablets treatment group were due to adverse events, accounting for 27% of the early discontinuations in contrast to 7% of the discontinuations from the placebo group. Thirty-four percent of the placebo-treated patients discontinued the study due to lack of efficacy compared to 15% of tramadol hydrochloride ER tablets-treated patients. The tramadol hydrochloride ER tablets group demonstrated a statistically significant decrease in the mean VAS score, and a statistically significant difference in the responder rate, based on the percent change

from baseline in the VAS score, measured at 1, 2, 4, 8, and 12 weeks, between patients receiving tramadol hydrochloride ER tablets and placebo (see Figure 4).

Figure 4



INDICATIONS AND USAGE

Tramadol hydrochloride ER tablets are indicated for the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time.

CONTRAINDICATIONS

Tramadol hydrochloride ER tablets should not be administered to patients who have previously demonstrated hypersensitivity to tramadol, any other component of this product or opioids. Tramadol hydrochloride ER tablets are contraindicated in any situation where opioids are contraindicated, including acute intoxication with any of the following: alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs. Tramadol hydrochloride ER tablets may worsen central nervous system and respiratory depression in these patients

WARNINGS

Seizure Risk

Seizures have been reported in patients receiving tramadol within the recommended dosage range. Spontaneous post-marketing reports indicate that seizure risk is increased with doses of tramadol above the recommended range. Concomitant use of tramadol increases the seizure risk in patients taking:

- **Selective serotonin re-uptake inhibitors (SSRI antidepressants or anorectics),**
- **Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.), or**
- **Other opioids.**

Administration of tramadol may enhance the seizure risk in patients taking:

- **MAO inhibitors (see also WARNINGS - Use with MAO Inhibitors and Serotonin Re-uptake Inhibitors),**
- **Neuroleptics, or**
- **Other drugs that reduce the seizure threshold.**

Risk of convulsions may also increase in patients with epilepsy, those with a history of seizures, or in patients with a recognized risk for seizure (such as head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections). In tramadol overdose, naloxone administration may increase the risk of seizure.

Suicide Risk

- **Do not prescribe tramadol hydrochloride ER tablets for patients who are suicidal or addiction-prone.**
- **Prescribe tramadol hydrochloride ER tablets with caution for patients taking tranquilizers or antidepressant drugs and patients who use alcohol in excess.**
- **Tell your patients not to exceed the recommended dose and to limit their intake of alcohol.**

Serotonin Syndrome Risk

The development of a potentially life-threatening serotonin syndrome may occur with use of tramadol products, including tramadol hydrochloride ER tablets, particularly with concomitant use of serotonergic drugs such as SSRIs, SNRIs, TCAs, MAOIs and triptans, with drugs which impair metabolism of serotonin (including MAOIs) and with drugs which impair metabolism of tramadol (CYP2D6 and CYP3A4 inhibitors). This may occur within the recommended dose. (See CLINICAL PHARMACOLOGY—Pharmacokinetics).

Serotonin syndrome may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

Tramadol products in excessive doses, either alone or in combination with other CNS depressants, including alcohol, are a major cause of drug-related deaths. Fatalities within the first hour of overdosage are not uncommon. Tramadol should not be taken in doses higher than those recommended by the physician. The judicious prescribing of tramadol is essential to the safe use of this drug.

With patients who are depressed or suicidal, consideration should be given to the use of non-narcotic analgesics. Patients should be cautioned about the concomitant use of tramadol products and alcohol because of potentially serious CNS-additive effects of these agents. Because of its added depressant effects, tramadol should be prescribed with caution for those patients whose medical condition requires the concomitant administration of sedatives, tranquilizers, muscle relaxants, antidepressants, or other CNS-depressant drugs. Patients should be advised of the additive depressant effects of these combinations.

Many of the tramadol-related deaths have occurred in patients with previous histories of emotional disturbances or suicidal ideation or attempts as well as histories of misuse of tranquilizers, alcohol, and other CNS-active drugs. Some deaths have occurred as a consequence of the accidental ingestion of excessive quantities of tramadol alone or in combination with other drugs. Patients taking tramadol should be warned not to exceed the dose recommended by their physician.

Anaphylactoid Reactions

Serious and rarely fatal anaphylactoid reactions have been reported in patients receiving therapy with tramadol. When these events do occur it is often following the first dose. Other reported allergic reactions include pruritus, hives, bronchospasm, angioedema, toxic epidermal necrolysis and Stevens-Johnson syndrome. Patients with a history of anaphylactoid reactions to codeine and other opioids may be at increased risk and therefore should not receive tramadol hydrochloride ER tablets (see **CONTRAINDICATIONS**).

Respiratory Depression

Administer tramadol hydrochloride ER tablets cautiously in patients at risk for respiratory depression. In these patients alternative non-opioid analgesics should be considered. When large doses of tramadol are administered with anesthetic medications or alcohol, respiratory depression may result. Respiratory depression should be treated as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures (see **WARNINGS** - **Seizure Risk** and **OVERDOSAGE**).

Interaction With Central Nervous System (CNS) Depressants

Tramadol hydrochloride ER tablets should be used with caution and in reduced dosages when administered to patients receiving CNS depressants such as alcohol, opioids, anesthetic agents, narcotics, phenothiazines, tranquilizers or sedative hypnotics. Tramadol hydrochloride ER tablets increases the risk of CNS and respiratory depression in these patients.

Increased Intracranial Pressure or Head Trauma

Tramadol hydrochloride ER tablets should be used with caution in patients with increased intracranial pressure or head injury. The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in these patients. Additionally, pupillary changes (miosis) from tramadol may obscure the existence, extent, or course of intracranial pathology. Clinicians should also maintain a high index of suspicion for adverse drug reaction when evaluating altered mental status in these patients if they are receiving tramadol hydrochloride ER tablets. (See **WARNINGS** - **Respiratory Depression**.)

Use in Ambulatory Patients

Tramadol hydrochloride ER tablets may impair the mental and or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

Use With MAO Inhibitors and Serotonin Re-uptake Inhibitors

Use tramadol hydrochloride ER tablets with great caution in patients taking monoamine oxidase inhibitors. Animal studies have shown increased deaths with combined administration. Concomitant use of tramadol hydrochloride ER tablets with MAO inhibitors or SSRIs increases the risk of adverse events, including seizure and serotonin syndrome.

Withdrawal

Withdrawal symptoms may occur if tramadol hydrochloride ER tablets are discontinued abruptly. These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely hallucinations. Clinical experience suggests that withdrawal symptoms may be reduced by tapering tramadol hydrochloride ER tablets.

Misuse, Abuse and Diversion of Opioids

Tramadol is an opioid agonist of the morphine-type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

Tramadol can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing tramadol hydrochloride ER tablets in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

Tramadol hydrochloride ER tablets could be abused by crushing, chewing, snorting, or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see **WARNINGS** and **DRUG ABUSE AND ADDICTION**).

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients.

Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Interactions with Alcohol and Drugs of Abuse

Tramadol may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

DRUG ABUSE AND ADDICTION

Tramadol hydrochloride is a mu-agonist opioid. Tramadol, like other opioids used in analgesia, can be abused and is subject to criminal diversion.

Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.

“Drug-seeking” behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated “loss” of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). “Doctor shopping” to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Tramadol hydrochloride ER tablets, like other opioids, may be diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Tramadol hydrochloride ER tablets are intended for oral use only. The crushed tablet poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances. With parenteral abuse, the tablet excipients can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Risk of Overdosage

Serious potential consequences of overdosage with tramadol hydrochloride ER tablets are central nervous system depression, respiratory depression and death. In treating an overdose, primary attention should be given to maintaining adequate ventilation along with general supportive treatment (see **OVERDOSAGE**).

PRECAUTIONS

Acute Abdominal Condition

The administration of tramadol hydrochloride ER tablets may complicate the clinical assessment of patients with acute abdominal conditions.

Use in Renal and Hepatic Disease

Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. Tramadol hydrochloride ER tablets have not been studied in patients with severe renal impairment (CLcr < 30 mL/min). The limited availability of dose strengths and once daily dosing of tramadol hydrochloride ER tablets does not permit the dosing flexibility required for safe use in patients with severe renal impairment. Therefore, tramadol hydrochloride ER tablets should not be used in patients with severe renal impairment (see **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**). Metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the liver. The pharmacokinetics of tramadol hydrochloride ER tablets has not been studied in patients with severe hepatic impairment. The limited availability of dose strengths and once daily dosing of tramadol hydrochloride ER tablets does not permit the dosing flexibility required for safe use in patients with severe hepatic impairment.

Therefore, tramadol hydrochloride ER tablets should not be used in patients with severe hepatic impairment (see **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

INFORMATION FOR PATIENTS

- Patients should be informed that tramadol hydrochloride ER tablets are for oral use only and should be swallowed whole. The tablets should not be chewed, crushed, or split.
- Patients should be informed that tramadol hydrochloride ER tablets may cause seizures and/or serotonin syndrome with concomitant use of serotonergic agents (including SRIs, NRIs, and triptans) or drugs that significantly reduce the metabolic clearance of tramadol.
- Patients should be informed that tramadol hydrochloride ER tablets may impair mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
- Patients should be informed that tramadol hydrochloride ER tablets should not be taken with alcohol containing beverages.
- Patients should be informed that tramadol hydrochloride ER tablets should be used with caution when taking medications such as tranquilizers, hypnotics or other opiate containing analgesics.
- Female patients should be instructed to inform the prescriber if they are pregnant, think they might become pregnant, or are trying to become pregnant (see **PRECAUTIONS - Labor and Delivery**).
- Patients should be educated regarding the single-dose and 24 hour dosing regimen, as exceeding these recommendations can result in respiratory depression, seizures or death.

Use in Drug and Alcohol Addiction

Tramadol hydrochloride is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia.

Drug Interactions

CYP2D6 and CYP3A4 inhibitors: Concomitant administration of CYP2D6 and/or CYP3A4 inhibitors (see **CLINICAL PHARMACOLOGY — Pharmacokinetics**), such as quinidine, fluoxetine, paroxetine and amitriptyline (CYP2D6 inhibitors), and ketoconazole and erythromycin (CYP3A4 inhibitors), may reduce metabolic clearance of tramadol increasing the risk for serious adverse events including seizures and serotonin syndrome.

Serotonergic Drugs: There have been postmarketing reports of serotonin syndrome with use of tramadol and SSRIs/SNRIs or MAOIs and α2-adrenergic blockers. Caution is advised when tramadol hydrochloride ER tablets are coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as SSRIs, MAOIs, triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, or St. John's Wort. If concomitant treatment of tramadol hydrochloride ER tablets with a drug affecting the serotonergic neurotransmitter system is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **WARNINGS – Serotonin Syndrome**).

Triptans: Based on the mechanism of action of tramadol and the potential for serotonin syndrome, caution is advised when tramadol hydrochloride ER tablet is coadministered with a triptan. If concomitant treatment of tramadol hydrochloride ER tablets with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **WARNINGS - Serotonin Syndrome**).

Use With Carbamazepine

Patients taking **carbamazepine**, a CYP3A4 inducer, may have a significantly reduced analgesic effect of tramadol. Because carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol, concomitant administration of tramadol hydrochloride ER tablets and carbamazepine is not recommended.

Use With Quinidine

Coadministration of **quinidine** with tramadol hydrochloride ER tablets resulted in a 50 to 60% increase in tramadol exposure and a 50 to 60% decrease in M1 exposure (see **CLINICAL PHARMACOLOGY - Drug Interactions**). The clinical consequences of these findings are unknown.

Use With Digoxin and Warfarin

Post-marketing surveillance of tramadol has revealed rare reports of digoxin toxicity and alteration of warfarin effect, including elevation of prothrombin times.

Potential for Other Drugs to Affect Tramadol
*In vitro*drug interaction studies in human liver microsomes indicate that concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine, and amitriptyline could result in some inhibition of the metabolism of tramadol.

Administration of CYP3A4 inhibitors, such as ketoconazole and erythromycin, or inducers, such as rifampin and St. John's Wort, with tramadol hydrochloride ER tablets may affect the metabolism of tramadol leading to altered tramadol exposure.

Potential for Tramadol to Affect Other Drugs
*In vitro*drug interaction studies in human liver microsomes indicate that tramadol has no effect on quinidine metabolism. *In vitro* studies indicate that tramadol is unlikely to inhibit the CYP3A4-mediated metabolism of other drugs when administered concomitantly at therapeutic doses. Tramadol is a mild inducer of selected drug metabolism pathways measured in animals.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY
No carcinogenic effect of tramadol was observed in p53(+/–)-heterozygous mice at oral doses up to 150 mg/kg/day (approximately 2-fold maximum daily human dose [MDHD] of 400 mg/day for a 60 kg adult based on body surface conversion) for 26 weeks and in rats at oral doses up to 75 mg/kg/day for males and 100 mg/kg/day for females (approximately 2-fold MDHD) for two years. However, the excessive decrease in body weight gain observed in the rat study might have reduced their sensitivity to any potential carcinogenic effect of the drug.
Tramadol was not mutagenic in the following assays: a bacterial reverse mutation assay using *Salmonella* and *E. coli*, a mouse lymphoma assay (in the absence of metabolic activation), and a bone marrow micronucleus test in mice. Mutagenic results occurred in the presence of metabolic activation in the mouse lymphoma assay. Overall, the weight of evidence from these tests indicates that tramadol does not pose a genotoxic risk to humans.
No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg/day in male and female rats (approximately equivalent to MDHD).

Pregnancy

Teratogenic Effects: Pregnancy Category C
Tramadol was not teratogenic at oral dose levels up to 50 mg/kg/day (approximately equivalent to MDHD) in rats and 100 mg/kg (approximately 5-fold MDHD) in rabbits during organogenesis. However, embryo-fetal lethality, reductions in fetal weight and skeletal ossification, and increased supernumerary ribs were observed at a maternal toxic dose of 140 mg/kg in mice (approximately 2-fold MDHD), 80 mg/kg in rats (2-fold MDHD) or 300 mg/kg in rabbits (approximately 15-fold MDHD).

Non-teratogenic Effects
Tramadol caused a reduction in neonatal body weight and survival at an oral dose of 80 mg/kg (approximately 2-fold MDHD) when rats were treated during late gestation throughout lactation period.

There are no adequate and well-controlled studies in pregnant women. Tramadol hydrochloride ER tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Neonatal seizures, neonatal withdrawal syndrome, fetal death and still birth have been reported during post-marketing reports with tramadol HCl immediate-release products.

Labor and Delivery
Tramadol hydrochloride ER tablets should not be used in pregnant women prior to or during labor unless the potential benefits outweigh the risks. Safe use in pregnancy has not been established. Chronic use during pregnancy may lead to physical dependence and post-partum withdrawal symptoms in the newborn (see **DRUG ABUSE AND ADDICTION**). Tramadol has been shown to cross the placenta. The mean ratio of serum tramadol in the umbilical veins compared to maternal veins was 0.83 for 40 women treated with tramadol HCl during labor.
The effect of tramadol hydrochloride ER tablets, if any, on the later growth, development, and functional maturation of the child is unknown.

Nursing Mothers
Tramadol hydrochloride ER tablets are not recommended for obstetrical preoperative medication or for post-delivery analgesia in nursing mothers because its safety in infants and newborns has not been studied. Following a single IV 100 mg dose of tramadol, the cumulative excretion in breast milk within sixteen hours post-dose was 100 mcg of tramadol (0.1% of the maternal dose) and 27 mcg of M1.

Pediatric Use
The safety and efficacy of tramadol hydrochloride ER tablets in patients under 18 years of age have not been established. The use of tramadol hydrochloride ER tablets in the pediatric population is not recommended.

Geriatric Use
Nine-hundred-one elderly (65 years of age or older) subjects were exposed to tramadol hydrochloride ER tablets in clinical trials. Of those subjects, 156 were 75 years of age and older. In general, higher incidence rates of adverse events were observed for patients older than 65 years of age compared with patients 65 years and younger, particularly for the following adverse events: constipation, fatigue, weakness, postural hypotension and dyspepsia. For this reason, tramadol hydrochloride ER tablets should be used with great caution in patients older than 75 years of age (see **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS
Tramadol hydrochloride ER tablets were administered to a total of 3108 patients during studies conducted in the U.S. These included four double-blind studies in patients with osteoarthritis and/or chronic low back pain and one open-label study in patients with chronic non-malignant pain. A total of 901 patients were 65 years or older. The frequency of adverse events generally increased with doses from 100 mg to 400 mg in the two pooled, twelve-week, randomized, double-blind, placebo-controlled studies in patients with chronic non-malignant pain (see **Table 2**).
Table 2: Incidence (%) of patients with adverse event rates ≥ 5% from two 12 week placebo-controlled studies in patients with moderate to moderately severe chronic pain by dose (N = 1811).

MedDRA Preferred Term	**Tramadol Hydrochloride ER Tablets**				Placebo (N=406) n (%)
	100 mg (N= 403) n (%)	**200 mg (N=400) n (%)**	**300 mg (N=400) n (%)**	**400 mg (N=202) n (%)**	
Dizziness (not vertigo)	64 (15.9)	81 (20.3)	90 (22.5)	57 (28.2)	28 (6.9)
Nausea	61 (15.1)	90 (22.5)	102 (25.5)	53 (26.2)	32 (7.9)
Constipation	49 (12.2)	68 (17.0)	85 (21.3)	60 (29.7)	17 (4.2)
Headache	49 (12.2)	62 (15.5)	46 (11.5)	32 (15.8)	43 (10.6)
Somnolence	33 (8.2)	45 (11.3)	29 (7.3)	41 (20.3)	7 (1.7)
Flushing	31 (7.7)	40 (10.0)	35 (8.8)	32 (15.8)	18 (4.4)
Pruritus	25 (6.2)	34 (8.5)	30 (7.5)	24 (11.9)	4 (1.0)
Vomiting	20 (5.0)	29 (7.3)	34 (8.5)	19 (9.4)	11 (2.7)
Insomnia	26 (6.5)	32 (8.0)	36 (9.0)	22 (10.9)	13 (3.2)
Dry Mouth	20 (5.0)	29 (7.3)	39 (9.8)	18 (8.9)	6 (1.5)
Diarrhea	15 (3.7)	27 (6.8)	37 (8.5)	10 (5.0)	17 (4.2)
Asthenia	14 (3.5)	24 (6.0)	26 (6.5)	13 (6.4)	7 (1.7)
Postural hypotension	7 (1.7)	17 (4.3)	8 (2.0)	11 (5.4)	9 (2.2)
Sweating increased	6 (1.5)	8 (2.0)	15 (3.8)	13 (6.4)	1 (0.2)
Anorexia	3 (0.7)	7 (1.8)	21 (5.3)	12 (5.9)	1 (0.2)

The following adverse events were reported from all the chronic pain studies (N=3108).
The lists below include adverse events not otherwise noted in **Table 2**.
Adverse events with incidence rates of 1.0% to <5.0%
*Eye disorders:*vision blurred
*Gastrointestinal disorders:*abdominal pain upper, dyspepsia, abdominal pain, sore throat
*General disorders:*weakness, pain, feeling hot, influenza like illness, fall, rigors, lethargy, pyrexia, chest pain
*Infections and infestations:*nasopharyngitis, upper respiratory tract infection, sinusitis, influenza, gastroenteritis viral, urinary tract infection, bronchitis
*Investigations:*blood creatine phosphokinase increased, weight decreased
*Metabolism and nutrition disorders:*appetite decreased
*Musculoskeletal, connective tissue and bone disorders:*arthralgia, back pain, pain in limb, neck pain
*Nervous system disorders:*tremor, paraesthesia, hypoaesthesia
*Psychiatric disorders:*nervousness, anxiety, depression, restlessness
*Respiratory, thoracic and mediastinal disorders:*sneezing, cough, rhinorrhea, nasal congestion, dyspnea, sinus congestion
*Skin and subcutaneous tissue disorders:*sweating increased, dermatitis
*Vascular disorders:*hot flashes, vasodilatation
Adverse events with incidence rates of 0.5% to <1.0% and serious adverse events reported in at least 2 patients.
*Cardiac disorders:*palpitations, myocardial infarction
*Ear and labyrinth disorders:*tinnitus, vertigo

*Gastrointestinal disorders:*flatulence, toothache, constipation aggravated, appendicitis, pancreatitis
*General disorders:*feeling jittery, edema lower limb, shivering, joint swelling, malaise, drug withdrawal syndrome, peripheral swelling
*Hepato-biliary disorders:*cholelithiasis, cholecystitis
*Infections and infestations:*cellulitis, ear infection, gastroenteritis, pneumonia, viral infection
*Injury and poisoning:*joint sprain, muscle injury
*Investigations:*alanine aminotransferase increased, blood pressure increased, aspartate aminotransferase increased, heart rate increased, blood glucose increased, liver function tests abnormal
Musculoskeletal, connective tissue and bone disorders: muscle cramps, muscle spasms, joint stiffness, muscle twitching, myalgia, osteoarthritis aggravated
Nervous system disorders: migraine, sedation, syncope, disturbance in attention, dizziness aggravated
Psychiatric disorders: euphoric mood, irritability, libido decreased, sleep disorder, agitation, disorientation, abnormal dreams
*Renal and urinary disorders:*difficulty in micturition, urinary frequency, hematuria, dysuria, urinary retention
*Respiratory, thoracic and mediastinal disorders:*yawning
*Skin and subcutaneous tissue disorders:*contusion, piloerection, clamminess, night sweats, urticaria
*Vascular disorders:*hypertension aggravated, hypertension, peripheral ischemia

OVERDOSAGE
Acute overdosage with tramadol can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, and death.
Deaths due to overdose have been reported with abuse and misuse of tramadol, by ingesting, inhaling, or injecting the crushed tablets. Review of case reports has indicated that the risk of fatal overdose is further increased when tramadol is abused concurrently with alcohol or other CNS depressants, including other opioids.
In the treatment of tramadol overdosage, primary attention should be given to the reestablishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.
While naloxone will reverse some, but not all, symptoms caused by overdosage with tramadol, the risk of seizures is also increased with naloxone administration. In animals convulsions following the administration of toxic doses of tramadol hydrochloride ER tablets could be suppressed with barbiturates or benzodiazepines but were increased with naloxone. Naloxone administration did not change the lethality of an overdose in mice. Hemodialysis is not expected to be helpful in an overdose because it removes less than 7% of the administered dose in a 4 hour dialysis period.

DOSAGE AND ADMINISTRATION
Tramadol hydrochloride ER tablets should not be used in patients with:
• creatinine clearance less than 30 mL/min,

• severe hepatic impairment (Child-Pugh Class C)

(See **PRECAUTIONS - Use in Renal and Hepatic Disease.**)
Tramadol hydrochloride ER tablets must be swallowed whole and must not be chewed, crushed, or split (see **WARNINGS - Misuse, Abuse and Diversion of Opioids** and **DRUG ABUSE AND ADDICTION**).

Adults (18 years of age and over)

Patients Not Currently on Tramadol Immediate-Release Products
For patients not currently treated with tramadol immediate-release (IR) products, tramadol hydrochloride ER tablets should be initiated at a dose of 100 mg once daily and titrated up as necessary by 100 mg increments every five days for relief of pain and depending upon tolerability. Tramadol hydrochloride ER tablets should not be administered at a dose **exceeding 300 mg per day.**

Patients Currently on Tramadol Immediate-Release Products
For patients maintained on tramadol IR products, calculate the 24 hour tramadol IR dose and initiate a total daily dose of tramadol hydrochloride ER tablets rounded down to the next lowest 100 mg increment. The dose may subsequently be individualized according to patient need. Due to limitations in flexibility of dose selection with tramadol hydrochloride ER tablets, some patients maintained on tramadol IR products may not be able to convert tramadol hydrochloride ER tablets. Tramadol hydrochloride ER tablets should not be administered at a dose **exceeding 300 mg per day.** The concomitant use of tramadol hydrochloride ER tablets with other tramadol products is not recommended (see **WARNINGS**).

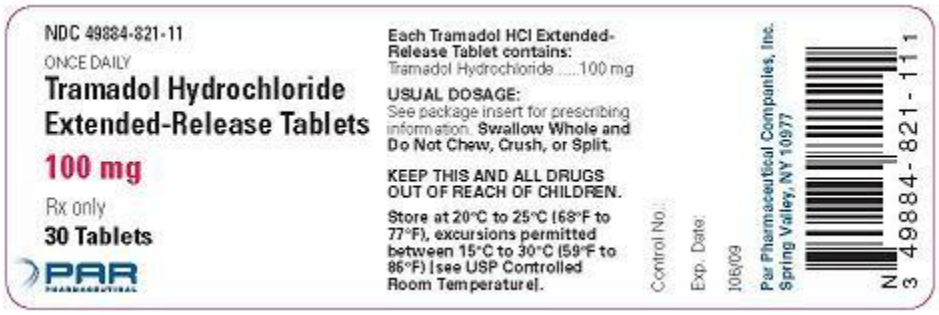
Individualization of Dose
Good pain management practice dictates that the dose be individualized according to patient need using the lowest beneficial dose. Start at the lowest possible dose and titrate upward as tolerated to achieve an adequate effect. Clinical studies of tramadol hydrochloride ER tablets have not demonstrated a clinical benefit at a total daily dose exceeding 300 mg.

In general, dosing of an elderly patient (over 65 years of age) should be initiated cautiously, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy. Tramadol hydrochloride ER tablets should be administered with even greater caution in patients over 75 years, due to the greater frequency of adverse events seen in this population.

HOW SUPPLIED

Tramadol hydrochloride extended-release tablets are supplied in the following package and dose strength forms:
100 mg, round, white to off-white tablets, imprinted with “Par821” on one side of the tablet in black ink
Bottle of 30 tablets – NDC 49884-821-11
Bottle of 90 tablets – NDC 49884-821-09
Bottle of 500 tablets – NDC 49884-821-05
200 mg, round, white to off-white tablets, imprinted with “Par822” on one side of the tablet in black ink
Bottle of 30 tablets – NDC 49884-822-11
Bottle of 90 tablets – NDC 49884-822-09
Bottle of 500 tablets – NDC 49884-822-05
Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
Manufactured by:
Par Pharmaceutical Companies, Inc.
Spring Valley, NY 10977
Issued: 06/09

PRINCIPAL DISPLAY PANEL - 100 MG, 30 TABLETS



PRINCIPAL DISPLAY PANEL – 200 MG, 30 TABLETS